

CLAIMS

1. A compound with affinity to human P-selectin, which is a derivative of a peptide or a functional equivalent of said peptide represented by $X(A_x)_m A_3 A_1 A_2 A_1 Y$, wherein:
- A_1 is a D- or L-cysteine (C), or a D- or L-valine (V), or an analogue thereof;
 - A_2 is D- or L-aspartic acid (D) or an analogue thereof;
 - A_3 is D- or L-phenylalanine (F), or a D- or L-tryptophan (W), or an analogue thereof;
 - A_x is D- or L-amino acid, selected from the group consisting of glutamic acid (E), aspartic acid (D), glycine (G) and cysteine (C);
 - X marks the N-terminal side of said sequence and is hydrogen or a residue comprising 1 to 6 D- or L-amino acids or analogues thereof;
 - Y marks the C-terminal side of said sequence and is -OH or a residue comprising 1 to 11 D- or L-amino acids or analogues thereof;
- wherein X and Y together may form a cyclic system;
- characterised in that at least one of X and Y or X+Y is substituted with the group $R^1-(Z)_n$ wherein:
- Z is selected from -CO-, -O-, -NR²-, and -CO-NR²- and wherein R¹ and R² are independently selected from:
- a) H;
 - b) a (C₁-C₈)alkyl group;
 - c) a (C₂-C₈)alkyl group, wherein at least one C-atom is replaced with a nitrogen-, oxygen- or sulphur atom;
 - d) a (C₆-C₁₄)aryl group, which may be substituted with at least one group selected from a halogen, (C₁-C₆)alkyl, -CF₃, -OH, -O-(C₁-C₆)alkyl, -COOH, -COO-(C₁-C₆)alkyl, -NO₂, -NH₂, -NH-(C₁-C₆)alkyl, -N-((C₁-C₆)alkyl)₂ and -SO₃H;
 - e) a heteroaryl group which is selected from 5- or 6-membered ring systems and benzo-condensed ring systems, and has at least one heteroatom selected from the group consisting of nitrogen, oxygen and sulphur, wherein said heteroaryl group may be substituted with at least one group selected from the group consisting of a halogen, (C₁-C₆)alkyl, -CF₃, -OH, -O-(C₁-C₆)alkyl, -COOH, -COO-(C₁-C₆)alkyl, -NO₂, -NH₂, -NH-(C₁-C₆)alkyl, -N-((C₁-C₆)alkyl)₂ and -SO₃H;

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f) an aralkyl group comprising an alkyl group as defined in b) or c) and an aryl group or heteroaryl group as defined in d) or e);

and wherein m and n are integers independently selected from 0 and 1, with the proviso that n is not 0 when R¹ is H.

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2. The compound according to claim 1, wherein A_x represents D- or L-glutamic acid (E) or D- or L- aspartic acid.

3. The compound according to claim 1 or 2, wherein A₁ represents D- or L-valine (V).

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4. The compound according to any one of the preceding claims, wherein A₃ is D- or L-tryptophan (W).

5. The compound according to any one of the preceding claims, wherein Y is a residue comprising D- or L- lysine.

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6. The compound according to any one of the preceding claims, wherein R¹ is unsubstituted phenyl or phenyl substituted with at least one substituent as defined in claim 1.

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7. The compound according to any one of the preceding claims, wherein n is 0 and R¹ is 3,4,5-trihydroxyphenylcarbonyl or 3,5-dicarboxyphenylcarbonyl.

8. The compound according to any one of the preceding claims, wherein X comprises no amino acids and Y comprises D- or L-lysine.

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9. The compound as claimed in claim 8, wherein n is 0 and R¹ is 3,4,5-trihydroxyphenylcarbonyl or 3,5-dicarboxyphenylcarbonyl.

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10. The compound of claim 1, wherein m is 0, wherein Z is -CO-, and wherein Z is attached to Y via a D- or L-glycine or aminobutyric acid spacer.

11. The compound according to any one of the preceding claims, comprising a cyclic or constrained backbone structure.
12. A composition comprising one or more derivatives of the peptides or functional equivalents thereof according to any one of the preceding claims.
13. A method for the preparation of a compound according to any one of any one of the preceding claims, comprising a sequence of steps wherein amino acid monomers, amino acid oligomers, or mono- or oligomers of amino acid analogues or mimetics are assembled by chemical or enzymatic ligation, and wherein said steps are performed in a liquid phase and/or at the interface to a functionalised solid phase.
14. The method according to claim 13, comprising reacting the HMPA linker of the formula 8 (Fig.1) by standard Fmoc chemistry to yield a compound of the sequence $X(A_x)_m A_3 A_1 A_2 A_1 Y$, wherein X, A_x , A_3 , A_1 , A_2 , Y and m are as defined in claim 1, and wherein the amino groups are initially protected by protecting groups, and R-CO is introduced by replacing the protecting groups by using standard methods.
15. Use of a compound according to any one of claims 1 to 11 as a medicine or diagnostic.
16. Use of a compound according to any one of claims 1 to 11 for the manufacture of a medicament for inhibiting leukocyte binding to platelets and/or endothelial cells.
17. The use according to claim 15 or 16 for the manufacture of a medicament for the treatment, prevention, or diagnosis of chronic inflammatory disorders, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, atherosclerosis, restenosis, ischemia, reperfusion injury including renal failure, tumour metastasis, bacterial sepsis, disseminated intravascular coagulation, adult respiratory stress syndrome, stroke, angiogenesis, transplant rejection, thrombosis, or circulatory shock.
18. Pharmaceutical composition, comprising a compound according to any one of claims 1 to 11 and one or more pharmaceutically acceptable carriers or excipients.

19. Pharmaceutical composition according to claim 18, which is formulated and processed for parenteral administration, preferably for intravascular, intramuscular, subcutaneous or intralesional injection.
- 5 20. Pharmaceutical composition according to claim 18, which is formulated and processed for oral administration, preferably in form of a tablet, a capsule, granules, an enteric solid dosage form, a solid dosage form providing sustained or controlled release or an orally disintegrating dosage form.
- 10 21. Pharmaceutical composition according to claim 18, which is formulated and processed for transmucosal administration, such as nasal, buccal, sublingual or vaginal administration.
22. Pharmaceutical composition according to claim 18, which is formulated and processed for pulmonary administration through a metered dose inhaler, a nebulizer, an aerosol spray
15 dispenser or a dry powder inhaler.
23. Pharmaceutical composition according to any one of claims 18 to 22, further comprising a drug targeting agent and/or a bioavailability enhancing agent.
- 20 24. A method for determining whether a molecule comprises a binding affinity for P-selectin comprising contacting P-selectin or a functional equivalent thereof with said molecule and with a compound according to any one of claims 1-11 and determining whether binding of said compound to said P-selectin or functional analogue thereof, is reduced.
- 25 25. A binding molecule capable of specifically binding a compound according to any one of claims 1-11.
26. A binding molecule according to claim 26, comprising an antibody or a functional
30 part, derivative and/or analogue thereof.
27. A method for determining whether a compound is capable of binding to human P-selectin, comprising substituting in a compound according to any one of claims 1-11, and

amino acid for a conservative amino acid and determining whether the resulting compound is capable of binding to said P-selectin.